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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,302	03/07/2001	Patrick F. Kelly	2427/1G685US1	2679

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	13

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,302	KELLY ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-37* is/are pending in the application.

4a) Of the above claim(s) *19-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-37 are pending in the application.

The Office Action is in response to the Amendment filed on 5/20/02.

Response to Amendment

The rejection of claims 1-18 under 35 U.S.C. 112, second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1, 2, 8, 12-14, 17 and 18 under 35 U.S.C. 102(b) has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 1-6, 8, 10-14, 17 and 18 under 35 U.S.C. 103(a) has been withdrawn in light of Applicants' amendment of the claims.

Claims 2-16 are rejected under 35 U.S.C.112, second paragraph for reasons as set forth below.

Claims 2-18 are rejected under 35 U.S.C.103(a) for reasons as set forth below.

Response to Arguments

In response to the restriction requirement, Applicants argue that claims 19 and 20 should be rejoined with group I because the claims were grouped with 17 and 18 in the Office Action mailed on 12/5/2001. In addition, Applicants point out since claims 15 and 16 are free of prior art, claims 19 and 20 should also be free of prior art because they recite same limitations. Applicants further argue that claims 21-30 recite the use of the stem cells of claim 17 and therefore should also be considered with elected claims.

The above argument has been fully considered but deemed unpersuasive. The invention of claims 19 and 20 are patentably distinct from the inventions of Group I (1-18) for reasons set

forth of the record mailed on 2/13/02. Although they are grouped with 17 and 18 in the Office Action mailed on 12/5/2001, claim 17 and 18 are joined with group I because Applicants' argument that the cells cannot be produced by other method was considered to be persuasive. However, claims 19 and 20 cannot be produced by the method of Group I without additional method steps. Therefore, they remain in Group II. Claims 21-30 are drawn to different methods of using the stem cells, they are patentably distinct from the invention of Group I for reasons set forth of the record mailed on 12/5/01. Therefore, the restriction requirement is maintained.

This application contains claims 19-37 drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claims 2, 3, 8, 12-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al., in view of Porter et al (1998, Journal of Virology, 72, no.3, p1769-1774).

The instant claims are drawn to a method of transducing stem cells with a vector containing a gene of interest, comprising contacting target stem cells with vector particles pseudotyped with RD114, and wherein the vector particles are substantially free of producer cells and producer cell supernatant. The claims are further drawn to said method transduced with an oncoviral particle (claim 8), and wherein the target stem cells are hematopoietic stem cells (12), wherein said hematopoietic stem cells are from cord blood, PMBC, bone marrow cells or liver cells (13), and wherein said hematopoietic cell are CD34+ or CE34+CD38- cells.

Onodera et al. teach that retroviral vector MPSV produced by packaging cell line FLYRD18 (pseudotyped with RD114) produced high titer viral particles (see Figure 4, page 1773). Onodera et al. also teach that transducing TJF-2 cells (B lymphoblastoid cell line) with supernatant (substantially free of producer cells, see method section) from FLYRD18 results in the highest ADA gene expression compare to supernatant from other packaging cell lines (see page 1773, 2nd col., last paragraph). Onodera et al. teach that MPSV-based retroviral vectors provide expression in immature progenitor cell types, therefore, may also be effective for gene therapy trials using hematopoietic stem cells (see page 1773, 2nd col., 2nd paragraph, lines 18-21). In addition, Onodera et al. teach that RD114 pseudotyped packaging cell lines have added advantage of being resistant to human complement (see page 1773, 2nd col., 3rd paragraph, bottom lines). Onodera et al. do not teach transduction of retroviral vectors pseudotyped with RD114 to hematopoietic stem cells.

Porter et al. teach the relative efficiency of transduction of bone marrow cells by retroviruses bearing the envelopes of amphotropic murine leukemia virus (MLV-A), xenotropic murine leukemia virus (MLV-X), gibbon ape leukemia virus (GALV), feline leukemia virus subgroup V (FeLV-B), and feline endogenous virus RD114 (see abstract). Porter et al. also teach that infection of bone marrow cells with a retroviral (oncoviral) vector comprising a lacZ gene and vector bearing MLV-A, GALV and RD114 envelope proteins is efficient as measured by lacZ expression in the transduced cells (see material and methods, *Generation of helper-positive and helper-free MFGnlacZ pseudotypes,* and page 917, table 3 and 4). Porter et al. further teach the CD34+ cells isolated from bone marrow are infected with similar efficiencies by packaging

with all those envelope proteins (see page 915, 2nd column, lines 1-3). Porter et al. also teach a population of stem cells transduced with vector particles pseudotyped with RD114 (see table 3).

It would have obvious to one of ordinary skilled in the art to combine the teaching of Onodera et al. and Porter et al. to develop a method of transducing hematopoietic stem cells with retroviral particle pseudotyped with RD114. Both articles teach that retroviral vectors pseudotyped with RD114 produces high titer and transduces cells efficiently. Although Onodera et al. does not provide an example of transduce hematopoietic stem cells, the article teaches that since MPSV-based retroviral vectors provide expression immature progenitor cells, they may be effective for gene therapy trials using hematopoietic stem cells. Porter et al. demonstrate that efficient transduction can be done in CD34+ bone marrow cells using RD114 pseudotyped vectors. Although Porter et al. teach that the transduction is accomplished by co-cultivation, it is not the only way to transduce these cells. Onodera et al. teach that efficient transduction using retroviral particles packaged with RD114 can be achieved with producer cell free viral particles. Therefore, it would have been obvious to one of ordinary skill in the art to transduce hematopoietic stem cells using retroviral particles pseudotyped with RD114 (either co-culture or substantially free of producer cells or supernatant). The ordinary artisan would have been motivated to do so since both articles teach effective transduction by such method, and the advantage of RD114 resistant to human complement. The ordinary artisan would have reasonable expectation of success because the teaching of both articles that cells (including hematopoietic stem cells) can be transduced efficiently by retroviral vectors pseudotyped with RD114. Therefore, the invention is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4-6 rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al., in view of Porter et al., as applied to claims 2, 3, 8, 12-14, 17 and 18 above, and further in view of Moritz et al. and Hanenberg et al (1996, Nature Medicine, Vol 2, no. 8, p876-882).

The claims are drawn to the method discussed above, wherein the vector particles are pre-absorbed to a surface with adherence promoting agent.

The teaching of Onodera et al. and Porter et al. are discussed above. However, both of the references do not teach the claimed method of transduction with vector particles pre-absorbed to a surface with adherence promoting agent.

Moritz et al. teach that fibronectin improves transduction of reconstituting hematopoietic stem cells by retroviral vector (see title). Moritz et al. also teach that such improvement is due to direct binding of retroviral particles to carboxyl-terminal chymotryptic fibronectin fragment, FN30/35 (see abstract and page 855, 1st column, 3rd paragraph, page 860, 2nd column, 3rd paragraph, lines 3-12). Moritz et al. further teach that cells are pre-stimulated with IL6, rhSCF and polybrene for 48 hours prior to retroviral infection (see page 856, second column, last two lines).

Hanenberg et al. teach that retroviral particles binding to CH-296, a portion of fibronectin that is made recombinantly in E coli. (Retronectin is a trademark name of CH-296 of fibronectin from Biowhittiker), produces most efficient transduction in both human or murine hemtopoietic cells (see page 880, 1st col., 1st paragraph, and Figure 2 and 3).

The obviousness to a method of transduce stem cells by using RD114 pseudotyped retroviral vector is discussed above. It would also have been obvious to one of ordinary skill of art to use an adherence-promoting agent such as retronectin to increase the transduction

efficiency of retroviral vector pseudotyped with RD114. The ordinary artisan would have been motivated to do so because of the teaching of both Moritz et al. and Hanenberg et al., both teach that fibronectin can improve transduction of hematopoietic stem cells, and also teach the specific portion that results in increased transduction efficiency. The ordinary artisan would have reasonable expectation of success also because both articles demonstrated increased transduction efficiency in hematopoietic cells using fibronectin. Therefore, the invention would have been obvious to one of ordinary skilled in the art at the time the invention was made.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al., in view of Porter et al., as applied to claims 2, 3, 8, 12-14, 17 and 18 above, and further in view of Moritz et al.

The claims are drawn to the method discussed above wherein the stem cells are pre-stimulated with growth factors, cytokines or phytohemagglutinin.

The teaching of Onodera et al., Porter et al., and Moritz et al. are discussed above. However, these references do not teach the method of transduction as discussed above, wherein the stem cells are pre-stimulated with cytokines, growth factors or phytohemagglutinin.

The obviousness to a method of transduce stem cells by using RD114 pseudotyped retroviral vector is discussed above. It would have been obvious to ordinary skilled in the art to pre-stimulate stem cells with cytokines, growth factors or phytohemagglutinin. The ordinary artisan would have been motivated to do because both Onodera et al. and Moritz et al. teach a efficient method of transduction wherein the cells are pre-stimulation with cytokines and growth factors (Moritz et al). The ordinary artisan would have reasonable expectation of success because of both articles demonstrated effective transduction of retroviral vectors by pre-stimulate

cells with cytokines. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al., in view of Porter et al., as applied to claims 2, 3, 8, 12-14, 17 and 18 above, and further in view of Rebel et al (30)

Claim 7 is drawn to the method discussed above, wherein the producer cells and producer cell supernatant by ultracentrifugation.

The teaching of Onodera et al. and Porter et al. are discussed above. However, both references do not teach the method discussed as above, wherein the producer cells and producer cell supernatant are removed by ultracentrifugation.

Rebel et al. teach a method of removing producer cells and producer cell supernatant and producing high titer retroviral particles by ultracentrifugation (see material and method, page 2218, 2nd col., 3rd paragraph, lines 7-12). Rebel et al. further teach that those concentrated retroviral particles is able to transduce bone marrow cells (see Figure 4, page 2221).

The obviousness to a method of transduce stem cells by using RD114 pseudotyped retroviral vector is discussed above. Removing producer cells and producer cell supernatant by ultracentrifugation is a routine method to concentrate retroviral particles as demonstrated by Rebel et al. Therefore, it would have been obvious to one of ordinary skill of art to practice the method of transducing stem cells with RD114 pseudotyped retroviral vectors that are substantially free of producer cell and producer cell supernatant, wherein the producer cells are removed by ultracentrifugation. The ordinary artisan would have been motivated to do so because said method would concentrate the viral particle and increase titer as taught by Rebel et

al. The ordinary artisan would have reasonable expectation of success because such method is provided in Rebel et al. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Onodera et al., in view of Porter et al., as applied to claims 2, 3, 8, 12-14, 17 and 18 above, and further in view of Unchida et al.

The claim is drawn to the method discussed above wherein the vector is a lentiviral vector.

The teaching of Onodera et al. and Porter et al. are discussed above. However, both references do not teach the method discussed above, wherein the retroviral vector is a lentiviral vector.

Uchida et al. teach lentiviral vector (HIV-1 based vector) mediate high efficiency gene transfer into highly purified hematopoietic stem cells (see abstract, and page 11944, 1st column, 2nd paragraph, lines 1-2, and page11941, figure 2C &E).

It would have been obvious to one of ordinary skill in the art to develop a method to improve transduction efficiency of hematopoietic stem cells using lentiviral vector pseudotyped with RD114 envelope. The ordinary artisan would have been motivated to do so because of the combined teaching of Onodera et al., Porter et al. and Uchida et al. Onodera et al. teach that retroviral vectors pseudotyped with RD114 and substantially free of producer cells are effective in transducing hematopoietic cells. Porter et al. also teach that retroviral vector pseudotyped RD114 envelope protein is efficient in gene delivery to stem cells with the added advantage of not being inactivated by human serum. Uchida et al. teach that using lentiviral vector in

transducing hematopoietic cells isolated from mobilized peripheral blood is efficient. The ordinary artisan would have a reasonable expectation of success of using such a transduction method because both Onodera et al. and Porter et al. demonstrate efficient gene transfer by viral vector psuedotyped with RD114 envelope protein, and Uchida et al. demonstrate that lentiviral vector improves transduction efficiency of hematopoietic stem cells over MLV vector. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2-16, the recitation "contacting" and "wherein the vector particles are substantially free of factors...and producer cell supernatant" renders the claims indefinite because it is unclear what the method steps encompass. In the response to election filed on 1/8/02, Applicants state that the method of transducing cells by co-culturing producer cells with target cells is same as contacting vectors with the targeting cells (see page 5). In the amendment filed on 5/20/02, Applicants imply that "substantially free of factors...and producer cell supernatant" should exclude co-culturing (see page 7). As such, it is unclear whether the claim encompass the step of co-culture. Amending claims so that they define the method steps clearly would overcome this rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
August 12, 2002

DAVID GUZO
PRIMARY EXAMINER